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(71) Applicant *(for all designated States except US)*: **CHEMPAQ APS** [DK/DK]; Symbion Science Park, Fruebjergvej 3, Box 38, DK-2100 Copenhagen Ø (DK).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **LARSEN, Ulrik, Darling** [DK/DK]; Kongevejen 191A, DK-2840 Holte (DK).

(74) Agent: **ALBIHNS A/S**; H.C. Andersens Boulevard 49, DK-1553 Copenhagen V (DK).

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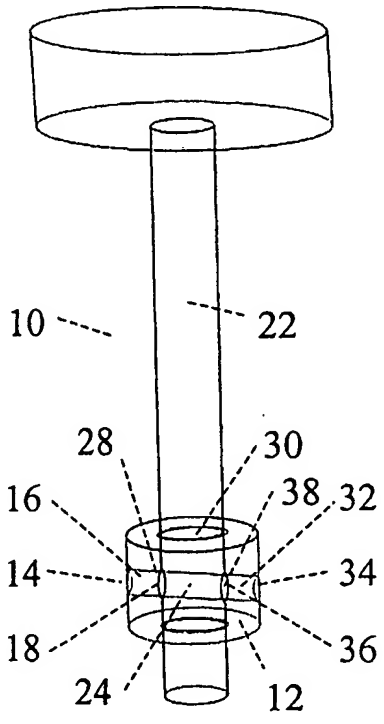
(54) Title: DEVICE FOR SAMPLING SMALL AND PRECISE VOLUMES OF LIQUID



(57) Abstract: A device is provided for sampling a small and precise volume of liquid, comprising a first member (12) with a first opening (14) for entrance of a liquid sample (26) into a first cavity (16) in the first member and with a second opening (18) for outputting the liquid sample from the first cavity. The first opening of the first member may be brought into contact with a liquid to be sampled so that the liquid may flow through the first opening into the first cavity and out of the second opening. The device further comprises a second member (22) movably positioned in relation to the first member and having a third opening (28) into a second cavity (24) for receiving and holding the liquid sample (26). During sampling of the liquid, the second member (22) is positioned in a first position in relation to the first member wherein the second opening (18) is in communication with the third opening (28) so that sampled liquid (26) may flow through the second and third opening into the second cavity (24). In a second position, the third opening (28) is disconnected from the second opening (18) so that the third opening is closed by the first member (12) whereby a precise volume of the sampled liquid is entrapped in the closed second cavity.

WO 02/089670 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DEVICE FOR SAMPLING SMALL AND PRECISE VOLUMES OF LIQUID

The present invention relates to precise sampling of small volumes of liquid, for example body liquids, such as blood, semen, saliva, spinal fluid, lymph, perspiration, urine, etc.

In order to determine the composition of a liquid, a sample of the liquid is typically subjected to various measurements, e.g. in order to determine the concentration of constituents of the liquid with a certain precision requiring that the withdrawn volume of the sample must be repeatable. With present sampling methods, the precision of the sample volume deteriorates as the volume become smaller; the smaller volume the poorer precision, thus leading to a low precision in concentration determination of constituents in the sample. For sample volumes less than 1 µL, this problem is significant; even high precision pipettes have a reasonably unrefined precision in this region. Typically, surface variations and dirt at the pipette tip cause relatively large variations in sampled volume. Another rather commonly used method for sampling of small volumes, typically in the order of 10-20 µL, is the use of capillary tubes. The liquid is drawn into the interior of the capillary tube by capillary action. Variations in the sample volume occurs due to variations at either end of the tube; at the sample-taking end of the capillary tube variations occurs due to liquid sticking; at the opposing end variations in the filling occurs due to small differences in the liquid surface tension at the end of the tube. These variations become even more significant when the required sample volume becomes smaller than 10 µL.

It is an object of the present invention to provide a device for sampling small volumes of liquid, such as volumes less than 1 to 10 µL, with a high precision.

According to the present invention, the above-mentioned and other objects are fulfilled by a device for sampling a small and precise volume of liquid, comprising a first member with a first opening for entrance of a liquid sample into a first cavity in the first member and with a second opening for outputting the liquid sample from the first cavity. The first opening of the first member may be brought into contact with a liquid to be sampled so that the liquid may flow through the first opening into the first cavity and out of the second opening. The device further comprises a second member with a second cavity for receiving and holding the liquid sample and having a third opening communicating with the second cavity. The second member may be movably positioned in relation to the first member. During sampling of the liquid, the second member is positioned in a first position in relation to the first member in which

first position, the second opening is in communication with the third opening so that sampled liquid may flow through the second and third opening into the second cavity. The third opening may be disconnected from the second opening in a second position of the second member in relation to the first member in such a way that the third opening is closed, e.g. by the first member, in the second position of the second member.

This entrapment of the liquid sample in the closed second cavity eliminates the effect of the variations in adherence and filling of liquid at sample device openings that is believed to cause the poor precision of small sample volumes in known liquid sampling devices and thus leads to a sampling device with an improved sampling precision.

Further, the first member may have a fourth cavity with fifth and sixth openings, and the second member may have a fourth opening so that, in the first position, the fourth opening communicates with the fifth opening, and the first opening communicates with the sixth opening so that the combined first and second cavities extends through the first and the second member and communicates with the environment through the first and the sixth opening. Thus, air may escape from the combined cavity through the sixth opening. Preferably, in the first position, a part of the liquid entering the second cavity may leave the second cavity through the fourth opening thereby ensuring that the second cavity is completely filled with liquid during liquid sampling whereby the risk of sampling with a reduced sample volume leading to low accuracy sampling is significantly reduced.

The second member may be inserted into the first member. For example, the first member may comprise a third cavity for receiving and accommodating at least a part of the second member.

The second member may have a cylindrical shape. A cylindrical shape facilitates displacement of the second member along a longitudinal axis of the cylinder. For example, a cylindrical second member may be inserted into a hole with a matching cross-section in the first member for displacement between the first and second position along a longitudinal axis of the second member.

The second member may have a circular cross-section, for example the second member may have a circular cylindrical shape. A circular cross-section facilitates displacement of the second member by rotation of the member around a centre axis of the circular cross-section. For example, a circular cylindrical second member may

be inserted into a matching circular hole in the first member for displacement between the first and second position along a longitudinal axis of the second member, or, by rotation around a centre axis of the circular cylinder, or, by a combination of the displacement and the rotation.

Liquid to be sampled may enter the cavities by any force causing a liquid flow, such as capillary action, diffusion, osmosis, pressure, suction, gravity, flow injection, liquid carrier, etc.

The first cavity may form a first capillary tunnel for entrance of a liquid sample by capillary attraction. The capillary tunnel is dimensioned so that, upon contact between the first opening and liquid to be sampled, a sample of the liquid is drawn into the first opening and the first capillary tunnel and the second opening by capillary attraction.

Further, the second cavity may form a second capillary tunnel adapted for drawing the liquid sample into the second cavity by capillary attraction. Preferably, the first and second capillary tunnel has the same diameter, and it is also preferred that, in the first position, the first and second capillary tunnel extend along substantially the same longitudinal centre axis.

In an embodiment of the present invention, the second member is rotatable about an axis of rotation that is substantially perpendicular to a longitudinal axis of the second cavity, and/or the second member may be displaced in a direction substantially perpendicular to a longitudinal axis of the second cavity.

The liquid sample may be brought into contact with another liquid after displacement of the second member, e.g. by emptying the second cavity through the fourth opening in the second member by any force causing a liquid flow, such as diffusion, osmosis, pressure, suction, gravity, flow injection, liquid carrier, etc.

Further, the liquid sample may be brought into contact with a selected liquid of a plurality of liquids after displacement of the second member into a corresponding selected position of a corresponding plurality of positions.

Preferably, the surface the first and second inner capillary tunnel walls is hydrophilic whereby the capillary attraction of the liquid sample is facilitated. For example, the inner tunnel walls may be made of e.g. glass or polymers, such as polystyrene.

Alternatively, the capillary tunnel walls may be made of another type of material and covalently or non-covalently coated with a hydrophilic material, such as a polymer or one or more reagents.

The capillary tunnel may also include one or more reagents adhered or chemically bonded to the inner tunnel wall. These reagents serve the purposes of further facilitating the capillary attraction of the sample and causing a chemical reaction in the liquid sample, e.g. introducing anticoagulant activity in a blood sample. Such reagents may comprise heparin, salts of EDTA, etc.

Preferably, the second member is made of a polymer.

For a better understanding of the present invention reference will now be made, by way of example, to the accompanying drawings, in which:

Fig. 1 shows schematically a preferred embodiment of the invention,

Fig. 2 shows schematically the operation of the embodiment shown in Fig. 1, and

Fig. 3 shows schematically the operation of another embodiment of the invention.

Fig. 1 schematically illustrates a device for sampling a small and accurate volume of liquid in accordance with the present invention. The device 10 comprises a first member 12 with a first opening 14 for entrance of a liquid sample (not shown) into a first cavity 16 in the first member 12 and with a second opening 18 for outputting the liquid sample from the first cavity 16. The first cavity 16 forms a capillary tunnel. The first opening 14 of the first member 12 may be brought into contact with a liquid 20 (shown in Fig. 2) to be sampled so that the liquid 20 may flow through the first opening 14 into the first cavity 16 and out of the second opening 18 by capillary attraction. The device 10 further comprises a second member 22 with a second cavity 24 for receiving and holding the liquid sample 26 (shown in Fig. 2) and having a third opening 28 communicating with the second cavity 24. The second cavity forms a capillary tunnel with the same diameter as the first cavity 16. The second member 22 is a circular cylinder that is movably positioned in relation to the first member 12. During sampling of the liquid, the second member 22 is positioned in the illustrated first position in relation to the first member 12 wherein the second opening 18 is in communication with the third opening 28 so that sampled liquid may flow through the second 18 and third opening 28 into the second cavity 24 by capillary attraction. The third opening 28 may be disconnected from the second opening 18 in a second position of the second member 22 in relation to the first member 12 so that the liquid sample 26 contained in the second cavity 24 is disconnected from the first cavity 16.

The second member 22 is inserted into a third cavity 30 of the first member 12 for receiving and accommodating a part of the second member 22. The second member

22 may be displaced between the first and second position along a longitudinal axis of the second member 22 that is also substantially perpendicular to a longitudinal axis of the second cavity 24. The second member 22 may also be rotatable about a longitudinal axis that is substantially perpendicular to a longitudinal axis of the second cavity 24. In the first position, the first 16 and second 24 capillary tunnels extend along substantially the same longitudinal centre axis.

Example 1: The capillary tunnel forming the second cavity 24 may have a length of 8 mm and a diameter of 0.9 mm for containing a liquid sample of 5.089 μL.

Example 2: The capillary tunnel forming the second cavity 24 may have a length of 5 mm and a diameter of 0.5 mm for containing a liquid sample of 0.982 μL.

Example 3: The capillary tunnel forming the second cavity 24 may have a length of 3 mm and a diameter of 0.3 mm for containing a liquid sample of 0.212 μL.

In the illustrated embodiment the first member 12 is symmetrical and has a fourth cavity 32 with openings 34, 36 opposite the first cavity 16, and the second member 22 has an opening 38 opposite the opening 28 so that, in the first position, a capillary tunnel extends through the first 12 and the second 22 member and communicates with the environment through openings 14, 36. Thus, air may escape from the capillary tunnel through opening 36. Further, in the first position, a part of the liquid entering the second cavity 24 will leave the cavity 24 through opening 38 thereby ensuring that the cavity 24 has been completely filled with liquid during liquid sampling eliminating the risk of sampling with a reduced sample volume leading to low accuracy sampling.

Fig. 2 schematically illustrates the operating principle of the embodiment of the present invention shown in Fig. 1. In Fig. 2a, the second member 22 is in its first position, and a sample of the liquid 20 is drawn into the capillary tunnel as described above with reference to Fig. 1. In Fig. 2b, the second member 24 has been displaced to its second position as indicated by the arrow 40, and in this position the liquid sample 26 may be brought into contact with another liquid, e.g. for analysing purposes. The container 42 may have a plurality of compartments containing different liquids so that the liquid sample 26 may be brought into contact with a selected liquid of a plurality of liquids after displacement of the second member 22 into a corresponding selected position of a corresponding plurality of positions.

Fig. 3 schematically illustrates another embodiment of the invention and its operating principle. The illustrated device 10 also includes a chamber 44 for storing a diluent for diluting the sample and a mixing chamber 46 for mixing the sample 26 and the diluent. Fig. 3a illustrates the device 10 ready for receiving the liquid. In Fig. 3b, a sample has entered into the capillary tunnel, and in Fig. 3c the second member 22 has been rotated into the second position for isolation of an accurate volume of the sample 26, and finally Fig. 3d illustrates that the sample 26 has been washed out of the capillary tunnel 24 and into the mixing chamber 46 by the diluent.

Although the principles of the present invention have been explained above with reference to a device utilising capillary attraction, it is obvious that the invention may as well be embodied in a syringe, a pipette, etc. The invention does not depend on the forces or principles utilised to introduce the liquid sample in the device. It is the gist of the invention that a part of the sampled liquid is entrapped with a high precision.

CLAIMS

1. A device for sampling a small and precise volume of liquid, comprising

a first member with a first opening for entrance of a liquid sample into a first cavity in the first member and with a second opening for outputting the liquid sample from the first cavity, and

a second member with a second cavity for receiving and holding the liquid sample and having a third opening communicating with the second cavity, the second member being movably positioned in relation to the first member in such a way that, in a first position, the second opening is in communication with the third opening for entrance of the liquid sample into the second cavity, and, in a second position, the third opening is closed.

2. A device according to claim 1, wherein the first member further comprises a third cavity for receiving and accommodating at least a part of the second member.

3. A device according to claim 1 or 2, wherein the second member has a cylindrical shape.

4. A device according to claim 3, wherein the second member has a circular cylindrical shape.

5. A device according to any of the preceding claims, wherein the first cavity forms a first capillary tunnel adapted so that, upon contact between the first opening and liquid to be sampled, a sample of the liquid is drawn into the first opening and the first capillary tunnel and the second opening by capillary attraction.

6. A device according to claim 5, wherein the second cavity forms a second capillary tunnel adapted for drawing the liquid sample into the second cavity by capillary attraction.

7. A device according to any of the preceding claims, wherein the second member is rotatable about an axis of rotation that is substantially perpendicular to a longitudinal axis of the second cavity.

8. A device according to any of the preceding claims, wherein the second member may be displaced in a direction substantially perpendicular to a longitudinal axis of the second cavity.

9. A device according to any of the preceding claims, wherein the liquid sample may be brought into contact with another liquid after displacement of the second member.

10. A device according to claim 9, wherein the liquid sample may be brought into contact with a selected liquid of a plurality of liquids after displacement of the second member into a corresponding selected position of a corresponding plurality of positions.

11. A device according to any of the preceding claims, wherein the second member is made of a polymer.

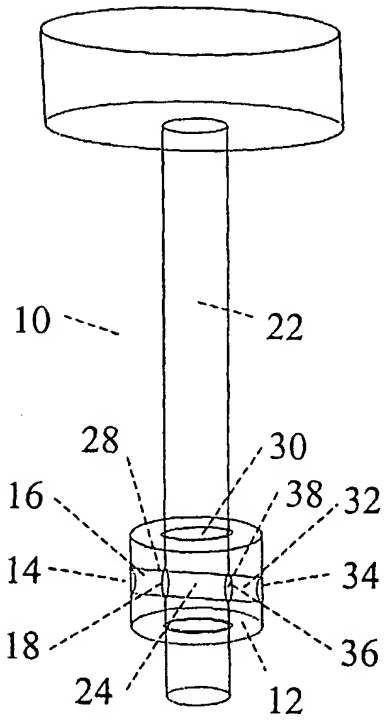


Fig. 1

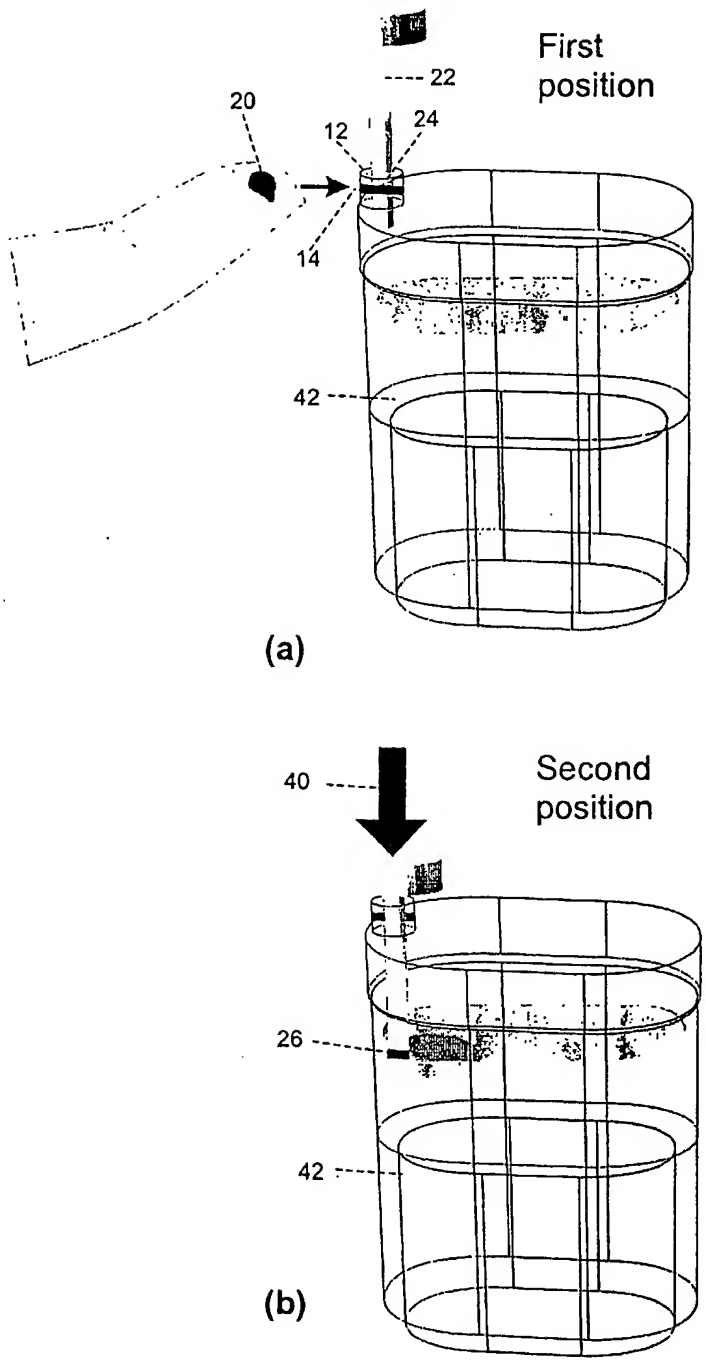


Fig. 2

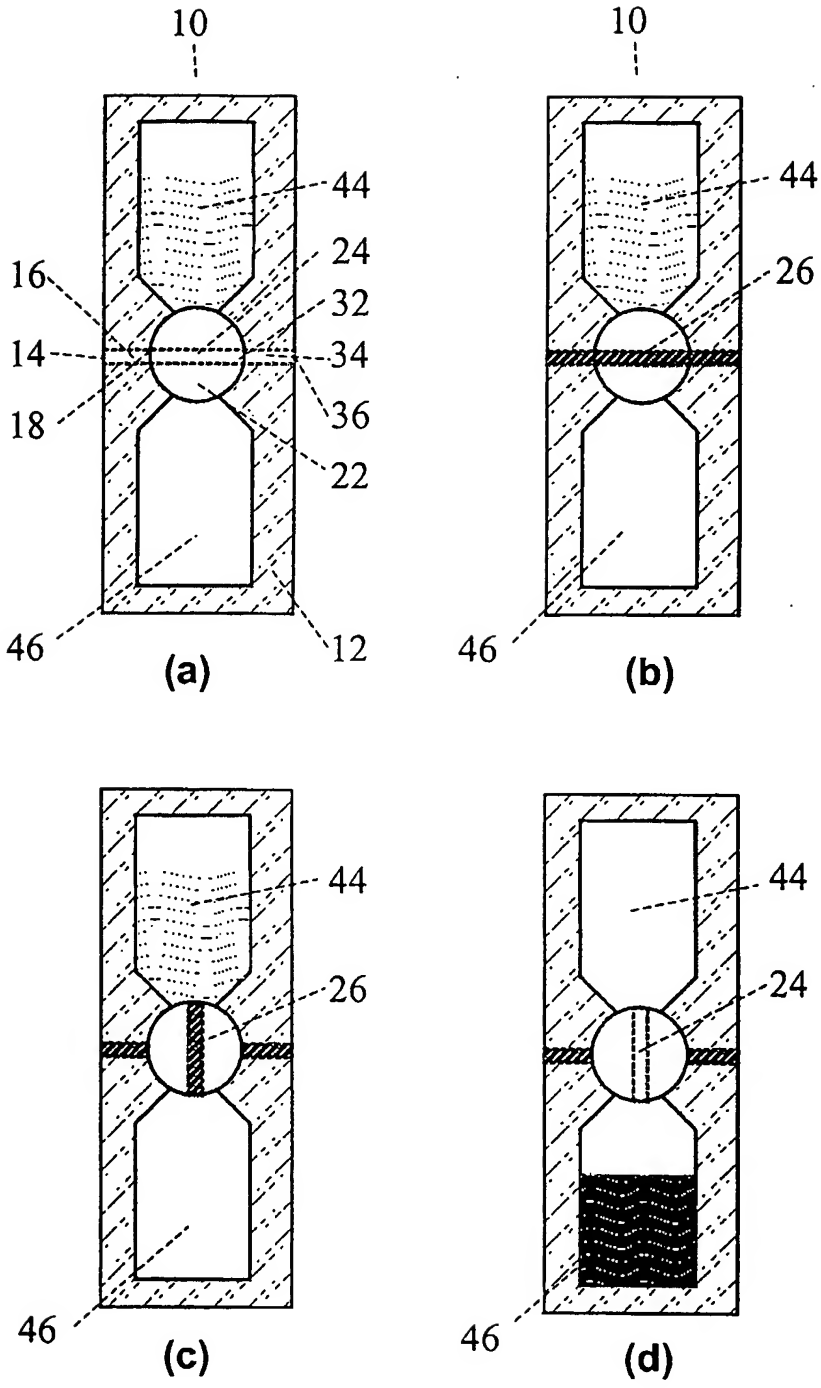


Fig. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/15 A61B10/00 B23K26/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B B01L B23K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	page 1, line 31 -page 2, line 22	7,8
Y	EP 0 005 979 A (DYNATECH AG) 12 December 1979 (1979-12-12) page 1, line 1 -page 6, line 13	1-6,9-11
Y	US 3 848 581 A (P. CINQUALBRE ET AL) 19 November 1974 (1974-11-19) column 1, line 38 -column 2, line 8; figure 4	1-6,9-11
Y	US 5 833 630 A (B. KLOTH) 10 November 1998 (1998-11-10)	1-6,9-11
A	column 4, line 66 -column 5, line 52	7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00292

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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